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ABSTRACT

The thousands of different drugs on the market can be separated into two categories: drugs that affect behavior, called psychoactive drugs, and drugs that do not affect behavior. Drugs get into the body by mouth, inhalation into the lungs, by injection into a vein, muscle or under the skin, and by absorption through mucous membranes. Regardless of the route most drugs must get into the circulatory system in order to travel to the target organ and exert an effect. Once in the circulation a drug must still pass several "barriers" before reaching its site of action and producing a change in behavior. Three of these barriers are the blood capillaries, the blood-brain barrier, and the placental barrier. The brain receives, integrates, and responds to sensory information it receives from peripheral organs and their receptors, and in addition is responsible for all cognitive functions. Changes in brain cells are responsible for all behavior, including those changes in behavior produced by psychoactive drugs. All psychoactive drugs produce their effects by altering the functional activity of neurotransmitters. Psychoactive drugs can increase or decrease the functional activity of various neurotransmitters. There are five major classifications of psychoactive drugs: stimulants, anti-psychotics, sedatives/hypnotics, opiates or narcotics, and psychedelics or hallucinogens. The termination of drug action is accomplished primarily by changing it to another molecular structure so that it is no longer an active agent or so that it can be removed from the body. Many psychoactive drugs can produce tolerance or dependence. (ABL)

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About the Author

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Drugs and the Brain
An Introduction to Neuropharmacology

by
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Center of Alcohol Studies
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Drugs and the Brain
An Introduction to Neuropharmacology

This booklet is an introduction to how drugs work. The field, pharmacology, includes the study of how drugs get into the body, exert their effects and are removed from the body. Neuropharmacology is a branch of pharmacology that focuses on drugs affecting the central nervous system.

WHAT TYPES OF DRUGS ARE THERE?

There are thousands of different drugs on the market. These can be separated into two categories: those that affect behavior and those that do not. Drugs that affect behavior are called *psychoactive* drugs. For example, alcohol, which affects behavior in many different ways, is a psychoactive drug. All psychoactive drugs alter behavior by changing one or another brain process.

Psychoactive drugs can be further categorized based upon the way in which they alter behavior. For example, there are five major categories of psychoactive drugs: *1.* stimulants, *2.* antipsychotics, *3.* sedative–hypnotics, *4.* narcotics or opiates and *5.* hallucinogens or psychedelics.

Although many commonly used non-psychoactive drugs, such as antibiotics (e.g., penicillin acts against bacterial infection) and anti-inflammatants (e.g., aspirin decreases swelling and inflammation) can alter behavior indirectly, they are not considered to be psychoactive. A drug that reduces the discomfort of a fever or infection enables the individual to get back on track and produces a feeling of well-being.

HOW DO DRUGS WORK?

In order for any drug to have an effect, it must get from the outside world into the body. There are several routes through which drugs can get into the body: by mouth, by inhalation into the lungs, by injection into a vein, muscle or under the skin, and by absorption through mucous membranes. Regardless of the route, most drugs must get into the blood (circulatory system) in order to travel to their target organ and exert an effect.

The Oral Route. The most common method of drug delivery is through oral administration, i.e., drugs are swallowed and enter the stomach (Figure 1). In the stomach, however, most drugs still will have no effect; they must get from the stomach to the small intestine or ileum where they are absorbed into the blood supply. In order for this to happen two conditions must be met. First, the drug must be water *soluble*; that is, it must be able to dissolve in water. Second, it

FIGURE 1

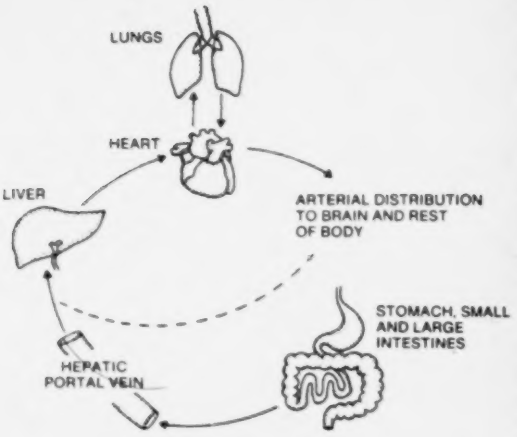

FIGURE 2

FIGURE 1.—The Common Route of Drug Administration. The most common route of drug administration is by mouth. Drugs are swallowed into the stomach and then pass into the small intestine or ileum. The rate at which drugs enter the circulation from the gastrointestinal tract depends largely on the presence of food in the stomach, solubility of the drug in water and its permeability through the walls of intestine.

FIGURE 2.—The Circulation of Drugs. Drugs pass into the circulation through blood vessels surrounding the ileum. Once in the circulation, the drug travels to the liver via the hepatic portal vein. From the liver, the drug continues to travel, in blood, to the right side of the heart, then, via the pulmonary artery, to the lung. Blood returning from the lung to the left side of the heart, via the pulmonary vein, is pumped throughout the body.

must be cell *permeable*, meaning it must be fat or lipid soluble so that it can pass through the cell membranes. If the drug is soluble in both water and lipid then small quantities of it can pass from the small intestine or ileum into surrounding, very small blood vessels called capillaries. Once in the capillaries of the circulatory system, the drug travels through the hepatic portal (liver transport) vein to the liver. From the liver the circulatory system returns to the heart where the drug, in the blood, is pumped to the lungs and then back to the heart and onward to the rest of the body. The entire blood supply makes its way around the body about every minute and eventually the drug is distributed to every organ and every cell in the body (Figure 2).

There are a number of advantages and disadvantages to the oral route. The main advantage of oral drug delivery is that it is easy. Also, in the event of an overdose or an immediate adverse reaction, the drug not yet absorbed in the stomach can be removed by pump-

ing the stomach or inducing vomiting. The disadvantages relate to the fact that not everyone can swallow pills: older, unconscious and vomiting patients may not be good candidates. Stomach acids and enzymes that aid in digestion may alter drug potency, and food contents may delay the absorption of drugs so that it will take longer for the drug to enter into circulation. Therefore, the dose that actually enters the circulation may be unknown.

The Pulmonary Route. Drugs that are inhaled enter the lungs and pass through the alveoli, small sacs in the lung that exchange gases. In order for a drug to pass through the alveoli into the circulation it must be in a gaseous form. The most common drugs entering through the pulmonary system are the volatile anesthetics used for surgery: halothane, metaphane and nitrous oxide (also called laughing gas) are a few examples of lipid soluble gases. Vapors from gasoline and certain cleaning agents and glue, smelling "salts," mouth inhalers (for asthma), marijuana and nicotine, the active ingredient in cigarettes, all enter the body via the lungs. The two major advantages of pulmonary administration are rapid onset of effects and ease of discontinuing administration. The drug enters the circulation almost instantly (Figure 2). Those who have had gas administered at the dentist's office know that within a few moments there is a loss of sensation and within a couple of minutes the dentist is drilling away. The other major advantage of this route is that once gas inhalation is discontinued, there is no further increase in the effect of the drug. It may, however, take some time for all of the drug to be removed from the body's muscle and fat tissue, depending on the anesthetic agent: hence, the use of a recovery room in hospitals for post-surgery patients.

Disadvantages of pulmonary administration may arise from undesired side effects. For example, the active ingredient in tobacco is nicotine, a drug easily absorbed from the lungs into the circulation. Unfortunately, bi-products of combustion (smoking) such as "tars" do not easily pass through the lungs: their chronic presence in lung tissue causes cancer.

The Injection Route. There are three major ways in which drugs can be injected into the body: intravenous, intramuscular and subcutaneous. With intravenous administration the drug is injected directly into the circulation, usually through a vein. It is the fastest method of drug administration available: since there is no delay between administration and entry into the circulatory system the effects are virtually immediate. The intravenous route is also known as i.v. or, for drug abusers, "mainlining."

Intramuscular administration is when a drug is injected into a large muscle, such as the upper arm or buttocks: the absorption time, usually 15 to 30 minutes, is considerably slower than the i.v. route.

Finally, there is the subcutaneous route, in which the drug is injected between the skin and underlying muscle (e.g., on the back of the hand). With drugs of abuse, it is sometimes called "skin popping." Like the intramuscular technique, absorption after subcutaneous injection can take 15 to 30 minutes.

The major advantages of drug administration by injection are that a very accurate dose can be given and it can be delivered to its site of action very rapidly. The disadvantages include overdose, since a large amount of drug is rapidly delivered and, in the event of a bad reaction, the drug cannot be recalled. There is also the problem of sterile syringes and hypodermic needles. If these are not sterile the user may contract an infectious disease such as hepatitis, AIDS, etc. Also, some individuals have a strong aversion to receiving injections, so this may be a disadvantage of sorts.

The Absorption Route. Drugs may also be administered by absorption from mucosal surfaces. For example, drugs may be absorbed through blood vessels in the vagina or rectum (suppositories), nose (nasal sprays) and mouth (heart medications such as nitroglycerine). This method provides a relatively simple way of taking drugs, which may have advantages in certain individuals, such as older patients who cannot swallow tablets or who have collapsed veins. The absorption of drugs through the mucous lining of the nose into blood capillaries in the nasal area is often used for illicit drugs (i.e., "snorting" cocaine or heroin).

Other Routes. Two other methods of drug delivery are worth mentioning because they are interesting and represent newer forms of drug delivery. The first is *transdermal*, literally, through the skin. Anti-seasickness medications can be placed on an adhesive disc, which is applied on the skin just behind the ear. The drug is absorbed through the skin to the vicinity of the inner ear (disturbances in the latter are responsible for seasickness). Heart medications can also be delivered through a transdermal patch applied to the chest every few days or longer. The second method involves the delivery of drug through the cornea, a clear layer covering the front of the eye. This method, called *trans-corneal* administration, is useful in treating glaucoma or other eye diseases.

DRUG DISTRIBUTION

The drug has now moved via several possible routes from the outside world into the body. Once in the circulation a drug must still pass several "barriers" before reaching its site of action and producing a change in behavior. These barriers take the form of different membranes. In a sense the membrane is like a thin shell that surrounds each cell of the body. Membranes give the cell its shape and keep certain cell parts from leaving the cell while it prevents other things outside the cell from entering.

All organs are made of cells, and all cells have a membrane. The barriers we will discuss in this section include blood capillaries, the blood-brain barrier and the placental barrier. For a drug to get into a cell and have an effect, it must first pass through the cell membrane. Membranes are made up of layers of proteins and lipids (fats) sandwiched together so that the protein layers form the outside and innermost walls of the membrane.

This sandwich of protein-lipid-protein provides a barrier which is permeable to some substances but impermeable to others. Alcohol passes through all membranes very easily, while opiates, well-known pain killers, pass through lipid membranes slowly.

Blood-Brain Barrier. The blood-brain barrier (BBB) acts to keep certain drugs and other compounds away from the brain by decreasing the permeability of capillaries in the region of the brain. It is this change in permeability of capillaries that results in a selective brain barrier. This change of permeability occurs because the BBB only allows drugs of a specific molecular size or those bound to special transport proteins to pass through into the brain. Compounds that are too large or not lipid soluble do not pass through the BBB. The change in permeability occurs because in the brain there is a unique arrangement between capillaries and special cells called astrocytes: the capillaries are surrounded by astrocyte cells so that permeability through the capillary is restricted (Figure 3).

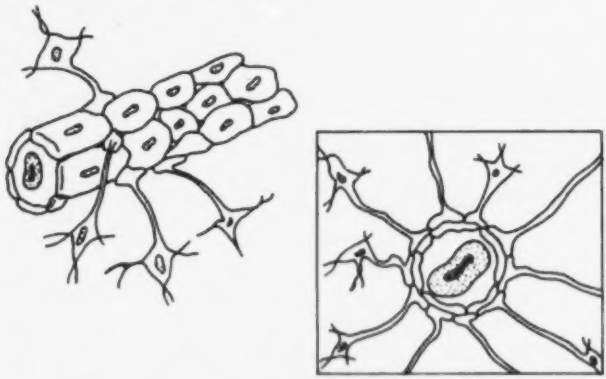

FIGURE 3

FIGURE 3.—The Blood-Brain Barrier. The Blood-Brain Barrier is a network of capillaries in the brain. Transport of certain drugs and other substances through the capillaries to brain cells is restricted by specialized cells—astrocytes—that form a sheath around the capillary. Astrocytes restrict drug transport by blocking small pores in the capillary wall through which these substances pass. The insert shows a single blood cell in a cross section of a capillary, surrounded by astrocytes.

Blood Capillaries. A capillary is a thin, tightly packed, single layer of cells. Between the cells that form capillaries are small pores which allow nutrients, water, and most drugs to pass out of the bloodstream and to the site of action, such as the brain, in the case of psychoactive drugs. Drugs, water and nutrients pass through the capillary wall based on a *concentration gradient*: the higher the concentration (amount per unit volume) inside the capillary, the greater the rate of diffusion from the capillary.

Which Drugs Pass Through the BBB?
Most drugs get into the brain fairly easily. All psychoactive drugs pass out of the circulation and reach brain cells, otherwise they would not have any effect. Not all drugs reach the brain though. Antibiotics such as penicillin do not. Therefore, brain infections that result from venereal and other infectious diseases cannot be treated with these drugs. Fortunately, the BBB tends to be very resistant to most infectious disease, preventing most bacterial and viral infections from reaching the brain. An interesting example of how to get through the BBB comes from treatment of Parkinson's disease, a central nervous system disorder that results in a progressive deterioration of motor control. A major biochemical mechanism in this disease is the deficiency of dopamine, a chemical messenger in the brain. Parkinson's disease cannot be treated by simply administering dopamine, because dopamine does not pass through the blood-brain barrier. Yet the disease is treatable. Scientists have learned that brain dopamine can be replenished by administering another chemical, L-dopa. L-dopa does pass through the BBB but, in the brain, it is converted into dopamine. Thus, the administration of L-dopa restores the chemical balance of dopamine in the brain and alleviates most of the symptoms of this disease.

Placental Barrier. This term is really a misnomer. Although the placental barrier is unique in that it separates two humans, it is not much of a barrier to drugs. The developing fetus receives nutrients and eliminates wastes through the placenta, and drugs also pass through the placenta quite freely so that the developing fetus is also exposed to whatever drugs the mother takes. This is an important fact to be aware of, since in the U.S. women take an average of four prescription drugs during pregnancy — not including over-the-counter medications, drugs in foods and consumables (caffeine, xanthines, nicotine) and exposure to various household and environmental chemicals. Scientists have not yet found all of the possible consequences of drugs on a developing fetus but three major types of effects are being studied: teratogenic, delivery and delayed.

Teratogenic effects refer to major morphological changes such as when a limb or organ, facial structure, etc., becomes grossly malformed. During the 1960's the use of the tranquilizer thalidomide during pregnancy was associated with a variety of birth defects such

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as incompletely developed limbs. There is now evidence that alcohol use during pregnancy also increases the risk of teratogenic defects. Alcohol, as well as other drugs, may produce teratogenic defects by directly altering the normal development of cells or by altering the transport of essential nutrients through the placenta to the fetus. Either of these effects may be due to the presence of the drug at a particular concentration or at a "critical" period during fetal development.

Drugs may also affect the normal delivery of a baby. Since newborns may not be able to metabolize or break down certain drugs, exposure to them may induce respiratory depression, anoxia or death. Finally, during pregnancy the use of several drugs, including alcohol, barbiturates, methadone and nicotine, is associated with a decrease in the birth weight. It is not yet known whether the changes found at birth (e.g., low birth weight) are associated with more subtle, delayed differences later in life.

THE TARGET OF PSYCHOACTIVE DRUGS

To understand how psychoactive drugs alter behavior it is helpful to first examine the basic elements of behavior. We respond to many events in our environment in many different ways. These events start out as purely sensory stimuli (visual, tactile, auditory, olfactory or gustatory), but in most cases a sensory stimulus "triggers" a cognitive association or mental response. A simple example of this is reading. First, letters and words on this page are nothing more than visual stimuli that fall on very specialized cells in the back of each eye, called receptors. The images activate entire fields of receptors in each eye and the information is then transmitted along the optic nerve to various parts of the brain, where it is further processed. In the brain, associations are made with previously stored information and some response is made. The responses can vary considerably from simply moving the eye to the next word (motor response), to prompting questions or forming a conclusion based upon what has been read (cognitive-behavioral response). The brain not only receives, integrates and responds to sensory information it receives from peripheral organs (eyes, ears, nose, tongue, skin) and their receptors and controls motor output, it is additionally responsible for all cognitive functions. Each and every fact, thought, belief, feeling and emotion we have ever experienced resides in the brain. How is this marvelous feat performed? The answer seems to be related to changes in functional activity in groups of brain cells. Thus changes in brain cells are responsible for *all* behavior, including those changes in behavior produced by psychoactive drugs.

How does the brain manage all of this? In part, the answer is in the specialization of the brain and the complexity of its nerve connections and neurocommunications. In order to appreciate how drug-induced changes in the normal activity of the brain alter behavior we need to first examine the "nuts and bolts" of the brain.

NEURONS, GLIA AND NEUROTRANSMISSION

The brain consists of two major types of cells called *neurons* and *glia*. Neurons are a specialized type of cell found only in the nervous system. Neurons transmit "information" about other parts of the body as well as the outside world via an electrochemical process. It is the change in this *functional activity*, the increase or decrease in the electrochemical activity of neurons, that produces behavior.

Different types of neurons form more specialized groups of brain structures called *nuclei* while other neurons form *fiber tracts* which interconnect various nuclei. Glial cells are primarily involved in the structural support of neurons and are involved in nutritive functions.

Figure 4A shows the human brain, Figure 4B shows a cross-section of the brain, from front to back, exposing several major nuclei. In a general sense, different nuclei are responsible for different behavioral and cognitive functions. For example, various portions of the cortex are devoted to specific functions involving motor control and vision; the left hemisphere of the cortex is involved in speech whereas the right cortex is involved in non-verbal imagery such as recognition. The hypothalamus regulates a number of pituitary hormones, eating, drinking and aggression; and the corpus callosum, a thick band of fiber tracts, transmits information from one side of the brain to the other.

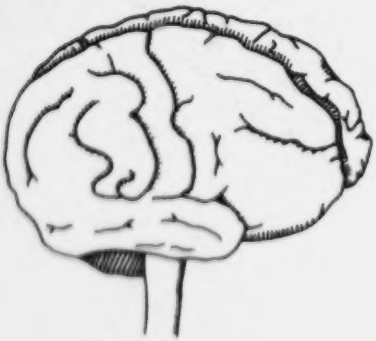

FIGURE 4A

FIGURE 4B

FIGURES 4A and 4B.—The Brain and a Cross-Section of the Brain. The human brain contains approximately 100 billion cells or neurons. Different types of neurons with specialized functions form different brain regions. Figure 4A shows an intact brain including frontal, parietal, temporal and visual cortex, brain stem and part of the cerebellum. Figure 4B shows the brain cut in half (mid-sagittal section) revealing many underlying differentiated brain structures. Many brain regions subserve very specific behavioral functions. Drugs alter behavior by affecting the normal functioning of different brain regions.

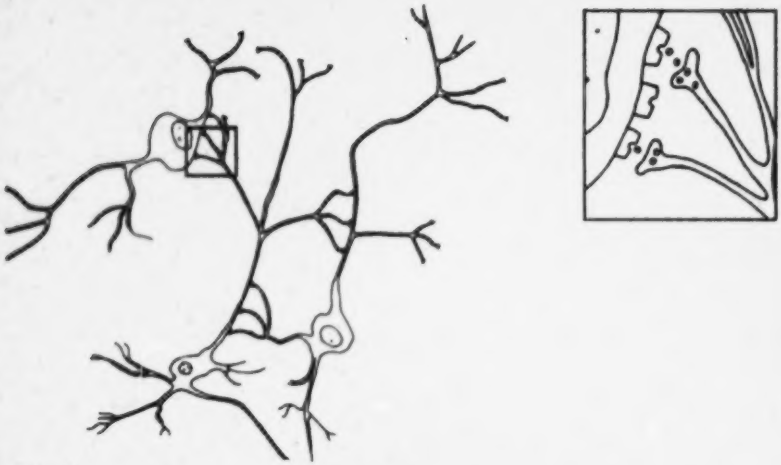

FIGURE 5

FIGURE 5.—An Illustration of Neurons and Neurotransmitter Activity. Three neurons—the basic type of brain cell—are shown. Neurons communicate with each other through neurotransmitters which are released from the end of the neuron (the axon terminal) into a small space (the synapse) between the axon terminal and neurotransmitter receptors located on an adjacent neuron. Psychoactive drugs alter behavior by changing neurotransmitter activity between and within neurons. The insert illustrates released neurotransmitter crossing the synapse and contacting specific receptors of another neuron.

Each nucleus is comprised of several hundred to several million neurons. To understand how the brain is affected by drugs we must first review how the basic unit of the brain, the neuron, is constructed and functions. Figure 5 shows the various parts of a neuron and the spatial relationship of three typical neurons. The branch-like processes that extend from each neuron almost touch adjacent neurons and their respective processes, but they are separated by a small space. This space is called a *synapse*. It is through the release of chemicals into the synapse that neurons communicate information to each other about the internal or external environment. In the brain a neuron might make contact with as many as 10,000 other neurons and the human brain contains approximately 100 billion neurons. Thus, our illustration is a very simplified representation of the complex arrangement of cells in the brain.

In order for a neuron to transmit its chemical message to another neuron, a series of events must take place, a process called *neurotransmission*. To begin with, neurons maintain an electrical charge called a *resting potential*. The resting potential of all neurons is negative in comparison to the charge outside the cell. The basis for this

negative charge is the distribution of salts and other substances in- and outside of the neuron. Neurotransmission starts with a change in the permeability of the cell membrane, in the region near the synapse, to certain ionized salts (salts dissolved or dissociated into solution form ions) such as sodium and potassium. For the most part, the outer membrane covering of the neuron keeps negatively charged potassium ions inside the cell and positively charged sodium ions outside the cell, resulting in the inside of the cell being negatively charged. Specialized biological "pumps" help maintain this balance of a negative resting potential. When the permeability of the membrane changes, sodium rushes into the neuron and potassium rushes out. If enough ions are exchanged, the resting potential inside the cell becomes positively charged, leading to a critical threshold that sets off the *action potential*. The action potential then travels down the length of the axon to the axon terminal. When the action potential reaches the axon terminal it causes the release of specialized chemicals that are stored there, inside vessicles. These chemicals are called *neurotransmitters*.

Where Do Neurotransmitters Go? Once released, the neurotransmitters enter into the synapse between neurons (Figure 5B). The neurotransmitter then comes in contact with *receptors* located on various parts of the next neuron — the post synaptic neuron. Depending on the particular type of neurotransmitter released, it will increase or decrease the probability of an action potential in that neuron. The process then continues or is temporarily stopped.

Eventually, after a fraction of a second, the neurotransmitter goes back into the synapse. Once back in the synapse the neurotransmitter is deactivated by enzymes or is often taken right back into the neuron from which it came through a process called "reuptake." As we shall see many psychoactive drugs alter the functional activity of neurotransmitters by altering the metabolizing enzymes or the reuptake process. This remarkable series of events which we call neurotransmission takes place in the brain many billions of times each second.

Chart 1 lists some of the more studied neurotransmitters along with several behavioral functions that scientists believe are mediated through these chemical messengers.

NEUROTRANSMISSION, DRUGS AND BEHAVIOR

All psychoactive drugs produce their effects by altering the functional activity of neurotransmitters. They may do this in several different ways. For example, increases in functional activity can be accomplished by: increasing release of a neurotransmitter; directly stimulating the receptors that the neurotransmitter stimulates; inhibiting the reuptake of the transmitter into the neuron (thus keeping it in the synapse where it is free to interact with receptors again); or

Chart 1. Some Neurotransmitters and Associated Behavioral Functions

Transmitter	In Brain
Acetylcholine	Learning, memory
Dopamine	Schizophrenia, vision, motor control, consummatory behavior
Endorphins	Pain, mental illness
Epinephrine	(Unknown)
Norepinephrine	Learning, memory, affective disorders, sleep, arousal, consummatory behavior
Serotonin	Sleep, mental illness, pain, consummatory behavior
Gamma-aminobutyric acid (GABA)	Anxiety

inhibiting enzymes in or near the neuron that would inactivate the neurotransmitter.

Similarly, psychoactive drugs can decrease the functional activity of various neurotransmitters by blocking receptors, decreasing neurotransmission, or decreasing manufacture or synthesis, or increasing reuptake or enzymatic breakdown.

Most psychoactive drugs have a *dose-response* relationship with behavior. As the concentration of the drug in the blood supply increases, so does the psychoactive action of the drug. As the concentration of drug in blood decreases, the effect on behavior also decreases. A dose-response curve is often used by pharmacologists to describe a particular drug effect. One way scientists express drug potency is in the dose required to produce a particular effect in some portion of the population. For example, if 10 milligrams was the effective dose (ED) required to produce a significant tranquilizing effect in 50% of the population this fact could be expressed as ED50 = 10 milligrams. Similarly, if 1,500 milligrams was the lethal dose (LD) of a drug that would kill 70% of the population this could be expressed as LD70 = 1500 milligrams.

MAJOR DRUG CLASSIFICATIONS

There are five major classes of psychoactive drugs: stimulants, antipsychotics, sedatives-hypnotics, opiates or narcotics, and psychedelics or hallucinogens. Listed below are some common examples of drugs in each of these five major classes, as well as a description of their mechanism of action. Chart 2 shows representative examples of drugs in each of the categories.

CHART 2.—Examples of the Five Major Classes of Psychoactive Drugs and their Behavioral and Pharmacological Actions

Classification	Behavioral and Pharmacological Actions
	STIMULANTS
General Stimulants:	
cocaine	Short-acting stimulant, increases feelings of well being, confidence, decreases fatigue, increases cardiac output. High doses may produce paranoia. *Crack*, a concentrated, more potent form of cocaine, may produce intense craving, addiction and unpredictable violent behavior. Blocks reuptake of norepinephrine.
amphetamine	Similar effects to cocaine but longer acting. Low doses increase alertness, euphoria, athletic performance, energy, decrease fatigue, but may also produce irritability, insomnia, increased cardiac output and anxiety. High doses may produce psychotic-like behavior. Development of tolerance and dependence variable. Increases functional activity of norepinephrine and dopamine.
methylphenidate (Ritalin)	Similar to amphetamine, more prominent effects on mental than motor activity, although high doses may cause convulsions. Increases transmission of norepinephrine.
Antidepressants:	
imipramine (Tofranil) amitriptyline (Elavil)	Reverses many forms of clinical depression, improves mood. Blockers of norepinephrine reuptake.
tranylcypromine (Parnate)	Reverses clinical depression, improves mood. Generally no effect in normal patients. Inhibits monoamine oxidase, an enzyme that metabolizes norepinephrine.
Convulsants:	
strychnine picrotoxin pentylenetetrazol (Metrozol)	Produce seizures and convulsions. Block inhibitory synapses in brain.
General Cellular Stimulants:	
caffeine theophylline	Increases alertness, produces clearer flow of thought; increases cardiac output, decreases fatigue, decreases reaction time. Tolerance and dependence may develop with repeated use. Increases the intracellular activity of neurons.
nicotine	May have both stimulant or depressant effects on heart. High doses may cause excess stimulation of respiratory system, convulsion or death. Stimulates certain receptors for the neurotransmitter acetylcholine.

CHART 2, cont.

Classification	Behavioral and Pharmacological Actions
	ANTIPSYCHOTICS
Phenothiazines:	
chlorpromazine	Improves mood in psychotic patients, reduces delusions and hallucinations, makes patient better candidate for therapy. Little or no tolerance or dependence. Dopamine receptor blockers.
Butyrophenones:	
haldol	
Lithium Salts:	Decrease norepinephrine release; increase norepinephrine uptake.
	SEDATIVE-HYPNOTICS
Barbiturates:	
sembutal seconal amytal pentothal	Behavioral disinhibition, decreases anxiety, produces sedation, drowsiness, depression, sleep and death with higher doses. Tolerance and physical dependence with repeated high doses. Unknown mechanism of action.
Antianxiety Agents:	
chlordiazepoxide (Librium) diazepam (Valium)	Decreases anxiety, tension, insomnia; less hypnotic (sleep producing) than barbiturates. Tolerance develops slowly. Unknown mechanism of action; may decrease serotonin activity.
meprobamate (Miltown)	Effects similar to barbiturates including relief from anxiety, sedation, sleep, tolerance and physical dependence. Mechanism of action unknown; may act through GABA.
Miscellaneous:	
ethanol (alcohol)	In low doses decreases anxiety, produces disinhibition and euphoria. High doses induce sedation, sleep and death by respiratory depression or aspiration of vomit. Tolerance and physical dependence with repeated high doses. Probably alters neuronal membranes to alter neurotransmission.
	OPIATES
opium morphine heroin meperidine methadone methyl-phenyl-tetrahydropyridine (MPTP)	Produce drowsiness, euphoric dreamlike state, indifference to pain. Effects vary considerably among users. Repeated use produces marked tolerance and physical dependence. Opiate receptor activation.

CHART 2, cont.

Classification	Behavioral and Pharmacological Actions
Miscellaneous: psyilocybin mescaline (peyote) lysergic acid diethylamide (LSD) phencyclidine (PCP) dimethoxy methamephetamine (STP, DOM) 3,4 methylene dioxyamphetamine (MDA) or methamphetamine (MDMA) (Ecstasy)	**PSYCHEDELICS** Produce wide variations in behavior including anxiety, confusion and sensory hallucinations depending upon drug. Tolerance but not physical dependence may develop with repeated use. Mechanisms of action vary considerably but include increases in the functional activity of acetylcholine (psyilocybin), norepinephrine (mescaline/peyote, MDA), serotonin (LSD), opiate receptors (PCP), dopamine (STP, DOM, PCP, MDA). MDA and MDMA may be neurotoxic (see text).

Stimulants. Drugs classified as stimulants generally produce a stimulation of behavior, such as increased alertness, sleeplessness, increased motor activity, increased intellectual functioning and feelings of well being. High doses of stimulants may produce stereotypic (repetitive) motor behavior or even psychosis (described in more detail below). Stimulants may also be used to treat severe, long-lasting depression, a clinical disorder characterized by a profound decrease in motivation, lack of interest or pleasure in things, disturbances in weight regulation, feelings of hopelessness and recurrent thoughts of death by suicide. Antidepressant drugs alleviate depression by increasing the functional activity of the noradrenergic system. The most common antidepressants block the reuptake of norepinephrine, thus enabling it to interact more with receptors in the synapse, or they inhibit an enzyme (MAO) that inactivates norepinephrine.

Antipsychotics. These drugs are used primarily to treat schizophrenia, a psychotic disorder characterized by loosening of associations and hallucinations. The schizophrenic may have broken from reality. The response to other people and situations is often inappropriate (e.g., laughing at the news of a family member's death), paranoid (e.g., belief that government agents or aliens are after them), catatonic (they may remain motionless, in awkward positions for extended periods of time); they cannot understand abstract concepts and tend to interpret things very literally (e.g., when asked to explain what it means when someone says "a stitch in time saves nine" a schizophrenic might give an answer having to do with sewing). The successful use of antipsychotic medications to treat these disorders suggests very strongly that the cause of these illnesses is due to a neurochemical imbalance or some other alteration in the functional activity of the systems on which these drugs work.

One of the most widely used antipsychotics is a class of drugs called phenothiazines. One of the often prescribed phenothiazines, chlorpromazine, alleviates psychotic behavior by decreasing the functional activity of two neurotransmitters, dopamine and norepinephrine. As the ability of the antipsychotic to block dopamine receptors increases, so does the psychotherapeutic effectiveness of the drug. Besides changing psychotic behavior, the blockade of dopamine receptors has other side effects. The long-term use of dopamine antipsychotics can result in tardive dyskinesia, a motor-function deficit with symptoms similar to Parkinson's disease. Dopamine is decreased in patients with Parkinson's disease. A decrease in the functional activity of dopamine occurs in both Parkinson's disease and with the long-term use of antipsychotic medications.

Sedative-Hypnotics. This category of drugs is capable of producing many kinds of behavioral depressions. There are a number of different types of sedative-hypnotics. The mechanisms of their action are not completely understood, but generally they produce a dose-dependent decrease in the functional activity of most brain neurons. Examples of the four major categories of sedative-hypnotics are shown in Chart 2.

In low doses, these drugs alleviate anxiety and produce disinhibition (in the case of alcohol); in moderate doses, they result in sedation and sleep; high doses can produce general anesthesia, coma and death from respiratory depression.

Unlike many psychoactive drugs, alcohol does not appear to act on specific receptors on neurons. Instead, alcohol affects the permeability of the entire neuron. This rather general pharmacological action may explain the very broad range of behavioral and medical consequences associated with alcohol use and alcoholism. In addition to alcohol-induced disinhibition and depression, single doses of alcohol decrease body temperature, visual perception, psychomotor performance, judgement and memory. Chronic alcohol use is associated with increased incidence of heart and liver disease and possible central nervous system damage.

Opiates. The term opiate refers to a class of narcotic drugs originally derived from the poppy plant. Opium, heroin and morphine are some of the most common opiates. The major uses of opiates are in the treatment of pain, diarrhea and cough. Morphine is the major pain-relieving agent found in opium (a resin exudate obtained from the poppy). Heroin does not occur naturally, but is a semisynthetic compound many times more potent than morphine. Totally synthetic opiates such as meperidine (Demerol) and methadone (Dolophine) are very potent analgesics. These drugs exert their psychoactive effects by interacting with specific opiate-like receptors located in the brain and other parts of the body.

In the early 1980's, a new type of heroin appeared on the illicit drug market, MPTP (methyl-phenyl-tetra-hydropyridine). This "designer" drug was synthesized by "bathtub" chemists to have properties similar to heroin, but it is different enough structurally so that, technically, it is not heroin and therefore not yet illegal. Recently a large batch of illicit MPTP was manufactured using a shortcut. The results were disasterous. Once inside the brain, this form of MPTP is metabolized to a potent neurotoxin which destroys dopamine neurons crucial to motor control. Addicts who used this MPTP very rapidly developed symptoms of advanced Parkinson's disease.

Subjectively, opiates have been reported to produce decreased response to pain, drowsiness, mood changes, feelings of warmth, peacefulness, contentment, a dreamlike state, and feelings of sexual gratification.

Psychedelics. Drugs that are classified as psychedelics or "mind-expanding" agents have the ability to induce visual, auditory and other sensory hallucinations. Hallucinogenic plants such as Peyote and *psilocybe* mushrooms have been used for centuries as part of religious ceremonies practiced by Mexican Indians and American Indians in the Southwestern United States. During the 1960's, the use of psychedelic drugs such as LSD reached its peak in the United States among the "turn-on, tune-in, drop-out" generation. The changes in perception of reality produced by these drugs are a result of changes in the functional activity of several neurotransmitter systems (see Chart 2). These drugs are capable of producing such vivid hallucinations that the recovery from a "bad trip" (one that produced acute paranoia and/or terror) sometimes takes months. The LSD of the 1980's, MDMA, also known as "Ecstasy," has effects similar to cocaine and psychedelic drugs without the intense visual hallucinations of the latter. A very similar hallucinogenic amphetamine is MDA, also known as "Love Drug." MDA and MDMA have neurotoxic effects. Recent evidence suggests that MDA selectively destroys brain cells containing the neurotransmitter serotonin.

RELATIONSHIP OF NEUROTRANSMITTERS TO BEHAVIOR

We can see from the previous section that changing the activity of specific neurochemical "messengers" can alter behavior. Recreational-type drugs alter normal behavior and therapeutic drugs restore behavior to normal. The use of pharmacological agents has been an invaluable tool in learning the way the brain works and how biochemical changes in the brain are responsible for behavior. For example, we now know that dopamine is an important neurotransmitter for motor behavior and mental health. At its simplest, too little dopamine can result in Parkinsonism, a disorder characterized by, among other things, uncontrollable tremor and loss of fine motor control. In schizophrenics, blocking of dopamine receptors significantly reduces the bizarre behavioral symptoms associated with this

disease, which along with other biochemical evidence suggests that part of the etiology of schizophrenia involves an abnormally active dopamine system. Chronic treatment of schizophrenia with dopamine blockers often results in tardive dyskinesia, a motor disorder similar to Parkinson's disease. Other neurotransmitters appear to have a role in mental functioning including sleep, arousal (serotonin, norepinephrine), learning and memory (norepinephrine, acetylcholine). Drugs that alter the functional activity of these neurotransmitters can be expected to significantly alter the behaviors mediated by these neurochemicals.

TERMINATION OF DRUG ACTION

The termination of drug action is accomplished primarily by changing it to another molecular structure so that it is no longer an active agent and/or so that it can be removed from the body. Two organs are primarily involved in the termination of drug action and the removal of drugs from the body, the liver and the kidneys.

Liver. The liver is a triangular shaped organ, located on the right side of the abdominal cavity. The liver breaks down or metabolizes drugs through the use of enzymes as the drug travels through the liver via the circulation. The metabolism of fat-soluble drugs results in the formation of water-soluble metabolites which can be excreted through urine. Usually, but not always, these metabolites do not have psychoactive properties.

Kidneys. The kidneys are bean-shaped organs, about the size of a fist. Each of the two kidneys is located in the rear of the abdominal cavity at the level of the lower ribs. The kidneys are the primary excretory organ of the body. Other organs, such as the lungs, skin, intestines and colon, also function as excretory organs, but to a lesser extent than the kidneys.

The kidneys perform two major functions. They remove products of liver metabolism and regulate the levels of most substances found in body fluids. Put simply, the kidneys get rid of unwanted substances in blood and retain the essential ones. This is accomplished by the primary unit of the kidney, the nephron. In each kidney, there are millions of nephrons that act to "filter" the bloodstream. As the filtered fluid passes through the kidney, unwanted substances pass into the urinary bladder for excretion.

TOLERANCE AND DEPENDENCE

Many of the psychoactive drugs we have discussed produce tolerance and dependence. Tolerance can be defined as a decrease in the responsiveness to the drug with continued exposure to the drug. With repeated use of a drug, especially when each exposure is close in time, the greater the development of tolerance. As tolerance develops, more and more of the drug is required to achieve the effect

obtained with the original dose. Several types of tolerance, described below, can develop with repeated drug use.

Acute tolerance develops with a single exposure to the drug. Acute tolerance is defined as a decrease in response to the drug during the descending portion of the blood drug concentration curve, compared to the response observed at the same blood concentration on the ascending limb of the drug concentration curve. In other words, there is a greater effect of the drug on behavior as the concentration of the drug is increasing in the blood compared to the same concentration when blood levels drop as a result of discontinued absorption and continued metabolism.

Chronic tolerance develops after repeated drug exposure. With repeated drug use the effect of the drug declines. This may be due to changes in the normal functioning of the cell or neuron. With time, the neuron adapts and changes characteristics of transmission to "normalize" the cell even though the drug is present. *Metabolic tolerance* refers to a decrease in the availability of the drug as a result of an increase in liver enzymes so that the drug is more rapidly metabolized.

Dependence is often associated with tolerance, but they are entirely different phenomena. A person who is physically dependent requires a drug to function "normally." The removal of the drug (abstinence) results in a "withdrawal syndrome." Withdrawal symptoms vary between drugs. For example, during alcohol withdrawal patients experience mental confusion, tremor, hallucinations and convulsions. The withdrawal syndrome usually begins six or more hours after the last drink and may last for days. Withdrawal from opiates is often described as an intense flu (fever, chills, weakness, gastrointestinal pain). Conversely, the readministration of the drug will alleviate withdrawal.

Both tolerance and physical addiction occur as a result of changes in the central nervous system. Although the precise mechanisms through which tolerance and dependence develop are not yet known, it is believed that changes in the functional activity of neurons play an important role in all behaviors, including tolerance and addiction. For many of the drugs we have discussed, these changes may occur in the receptors, but for other drugs, such as alcohol, tolerance and dependence may develop as a result of an alteration in the membranes that form neurons. Changes in membrane fluidity (and therefore, the flow of ions) may alter the functional activity of neuronal systems mediating various behaviors. Although considerable progress has been made in our understanding of how many drugs enter the body, exert their psychoactive effect, and have their activity terminated, additional basic research is needed to understand the neurochemical mechanisms involved in the development of tolerance and dependence.

Suggested Readings

Gilman, A.G., Goodman, L.S., Rall, T.W. and Murad, F. (Eds.) *Goodman and Gilman's The Pharmacological Basis of Therapeutics*. 7th Edition. New York: Macmillan; 1985.

Leavitt, F. *Drugs and Behavior*. 2nd Edition, Wiley Series on Personality Process, New York, 1982.

Ray, O.S. *Drugs, Society and Human Behavior*. 3rd Edition. St. Louis: Mosby; 1983.

About the Center of Alcohol Studies

The Center of Alcohol Studies was founded at Yale University in 1940. The center has been a leader in the interdisciplinary research on alcohol use and its effects and has been in the forefront of the movement to recognize alcoholism as a major public health problem. Dr. E.M. Jellinek was the center's first director, and the prestigious *Journal of Studies on Alcohol*, still published by the center, was founded by Howard W. Haggard, M.D. In 1962, the Center of Alcohol Studies moved to Rutgers University.

The center faculty have been trained in biochemistry, economics, physiology, psychology, psychiatry, sociology, political science, public health, education, statistics and information science. The faculty teach undergraduate, graduate and continuing education courses, including the world famous Summer School of Alcohol Studies. The SSAS alumni have assumed leadership positions in research, prevention and treatment of alcohol problems.

The center's major areas of concern are: research, education, treatment and prevention. The center maintains the foremost research library in the field to support these activities. As part of the center's educational mission, this pamphlet series presents information on important topics in the alcohol studies field.